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### Thrombolytic treatment for elderly patients

**Citation for published version:**

Elder, AT & Fox, KA 1992, 'Thrombolytic treatment for elderly patients', *British Medical Journal (BMJ)*, vol. 305, no. 6858, pp. 846-7.

**Link:**

[Link to publication record in Edinburgh Research Explorer](#)

**Document Version:**

Publisher's PDF, also known as Version of record

**Published In:**

British Medical Journal (BMJ)

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Each new study builds on its predecessors, providing new information, which aids the fine tuning of treatment. In the case of hypertension in elderly patients this includes the blood pressure levels at which to treat, the target blood pressure, upper age limits, how to manage other cardiovascular risk factors, and the use of newer drugs such as calcium antagonists and angiotensin converting enzyme inhibitors.

For combined systolic and diastolic hypertension the trial data suggest that treatment should be started at pressures above 160/90 mm Hg, and the target should be to lower both systolic and diastolic pressures below these levels. Similarly, in isolated systolic hypertension 160 mm Hg should be taken as the threshold, though recommendations regarding isolated systolic hypertension must be tentative pending confirmation from the Syst-Eur trial. Although a cautious approach to implementing the results of recent landmark studies may be wise, inaction cannot be justified in the face of the substantial body of information pointing towards the need to treat raised blood pressure in elderly patients.

One is led inevitably to the conclusion of Fotherby and colleagues that authoritative, clear guidelines for managing this common disorder are needed and that such guidelines should be revised regularly. Who should be responsible? The British Hypertension Society has produced useful guidelines on treating mild hypertension and is currently reviewing

them. Perhaps it should set itself the task of doing this both for hypertension in general and hypertension in elderly patients in particular, reviewing its guidelines biennially.

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## Thrombolytic treatment for elderly patients

### *Age is not a contraindication*

The risk of having a myocardial infarction and of dying as a result increases with age: about 80% of fatal myocardial infarctions in Britain occur in patients over 65.<sup>1</sup> A 75 year old with an acute myocardial infarction is seven times more likely to die in hospital than a patient aged 50, and mortality remains twice that of younger patients after discharge.<sup>2</sup>

Why is the mortality so much greater in elderly people? Conditions such as heart failure, angina, diabetes, and hypertension coexist more frequently, and all contribute to a poorer outcome.<sup>2</sup> So does increased age itself<sup>3</sup> and possibly the altered cardiac and systemic responses to myocardial infarction described in elderly patients.<sup>3</sup> Another reason, however, is that they are often treated differently from younger patients.<sup>3,4</sup>

Several studies have shown that thrombolytic treatment reduces mortality and morbidity after acute myocardial infarction<sup>5-9</sup> and, although not designed to assess the efficacy or safety of treatment in elderly patients, their results agree: thrombolytic agents produce the greatest reductions in absolute mortality in those at highest risk of death—particularly older patients. For example, in the second international study of infarct survival (ISIS-2) combined treatment with streptokinase and aspirin saved 10 lives for every 1000 patients treated aged under 60 but 47 lives for every 1000 patients over 70.<sup>7</sup>

Such benefit from thrombolysis depends on prompt administration, ideally within six hours of the onset of symptoms. Compared with other patients with myocardial infarction, elderly patients are more likely to present late, be difficult to diagnose, and have absolute contraindications to thrombolysis. Some must therefore be excluded from treatment,<sup>10,11</sup> and the prescription rate of thrombolytic agents in elderly patients should not be expected to equal that in younger

patients. Evidence exists, however, that some older patients are left untreated for less clearly justifiable reasons.

A recent survey of coronary care units in Britain suggested that 40% set an upper age limit for the use of thrombolysis and 20% excluded patients from coronary care, where thrombolysis is usually given, on the grounds of age alone.<sup>12</sup> Even in coronary care units not operating a formal age policy, thrombolysis is used less than in younger patients, often for poorly defined reasons. Experience in North America seems similar: one study showed that a patient aged 75 with no contraindications to thrombolysis had only half the chance of a similar patient aged 40 of receiving treatment.<sup>4</sup> Perhaps audit, which has already been used to identify and minimise inappropriate underuse, can improve matters.<sup>13</sup>

Why is the use of thrombolysis apparently restricted on the grounds of age? Cost effectiveness is at least as good as in younger patients.<sup>14,15</sup> Apprehension regarding the risk of haemorrhagic complications persists and may discourage some doctors from giving thrombolytic drugs to older patients. The risk of stroke at or around the time of myocardial infarction increases with age—to 1.1% in patients aged over 75 who are untreated and to 1.7% in those of similar age who receive thrombolysis.<sup>16</sup> This level of risk—six strokes per 1000 patients treated in this age group—is, however, far from that required to negate the overall benefits of thrombolytic drugs on mortality and morbidity in elderly patients.

Other concerns may exist. How might thrombolysis affect other important end points such as symptoms, function, and dependence? Will the early benefits on mortality be offset by a greater requirement for relatively high risk interventional treatment? Current research suggests not.<sup>17</sup>

Ultimately, decisions regarding the appropriate use of thrombolysis in older patients can become rational only if

studies are analysed not only by patients' ages but also according to their functional state and the presence of co-existent disease. At present, age is too frequently used as a convenient but inaccurate proxy for other, less easily measured indices of likely benefit and possible risk.

Clear reasons exist for treating elderly patients with thrombolytic agents: lives can be saved and myocardial function improved. We should ensure that the reasons for withholding treatment are equally clear. Age alone is not sufficient.

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# Treating psoriasis with calcipotriol

## Early studies are promising

Psoriasis is a chronic and distressing disease of uncertain aetiology which can be hard to treat. There is no cure. Topical measures such as tars and dithranol are of limited effect and acceptability, and steroids, although addictive to both patients and prescribers, have their well known hazards. Oral agents all have side effects and limitations.<sup>1</sup> An obvious gap therefore exists in the armoury of available treatments.

Sunlight and ultraviolet B radiation work in some cases of psoriasis, and their benefits have been attributed to increased production of cholecalciferol in the skin.<sup>2</sup> Treatment of osteoporosis with 1 $\alpha$ -cholecalciferol showed improvement in coincidental psoriasis, and one study found that cholecalciferol helped patients with psoriasis.<sup>3</sup> A larger study could not confirm this, possibly because the dose was too small.<sup>4</sup> The problem is that giving a large enough dose to overcome the resistance to the antiproliferative activity of 1,25-dihydroxycholecalciferol in patients with psoriasis<sup>5</sup> carries the risks of hypercalcaemia and calciuria: hence the search for analogues of cholecalciferol for topical use.

Calcipotriol is one such drug.<sup>6</sup> Early studies have shown that it is at least as effective as betamethasone,<sup>7</sup> if not more so<sup>8</sup>; and it is superior to short term dithranol.<sup>9</sup> Patients seem to like it, and it can be used for up to a year. Further experience of its use has been encouraging, and official approval has followed.<sup>10</sup> A paper in this week's journal extends its use to pustular psoriasis, which can be very difficult to manage and has an appreciable mortality (p 868).<sup>11</sup>

The benefits of calcipotriol are ease and tolerability of use—the cream is colourless and invisible on the skin and does not stain. The lack of colour and smell appeals to patients, many of whom have had bad experiences with tars and dithranol. It clears chronic plaques at a varying rate, and the benefits usually appear in two to three weeks. Its use on the face is not recommended as it produces soreness in most patients and perioral dermatitis in about 4%.<sup>9</sup> There is little experience of its use on flexures; some patients may not tolerate it. Many patients experience irritation and soreness in both chronic plaques and the normal skin around them, which increases

with time. My own experience suggests that discomfort and poor tolerance of calcipotriol occur mainly in three groups: fair skinned patients who burn easily in the sun; patients who have recently had courses of etretinate, which increases skin sensitivity; and patients who have been treated with strong corticosteroids long term.

Although calcipotriol's makers recommend its use for only six weeks followed by a gap, there are reports of safe use for a year.<sup>10</sup> The discomfort settles quickly when calcipotriol is withdrawn, and it can usually be reintroduced later without problem. Patients need to be careful about exposure to the sun, but so do many patients with active psoriasis. The maximum recommended amount is 100 g a week to minimise the theoretical risk of hypercalcaemia. Calcipotriol is rapidly inactivated, however, and has a much smaller effect on calcium metabolism than 1,25-dihydroxycholecalciferol.<sup>12 13</sup> Extensive or unstable disease could alter the absorption of calcipotriol, so it is interesting that up to 300 g has been given in 10 days without problem.<sup>11</sup> These doses were given to sick patients in hospital who were being carefully monitored. The theoretical possibility of resorption of bone has not been confirmed clinically.<sup>8</sup> Long term studies may show problems, but as yet the prospects are optimistic and calcipotriol is already widely accepted.

Calcipotriol's mode of action is still unclear. Proliferation of epidermal keratinocytes (one of the hallmarks of psoriasis) is reduced and terminal differentiation increased.<sup>8</sup> Inflammation is reduced as is the activity of ornithine decarboxylase. This enzyme suppresses proliferating T lymphocytes,<sup>1</sup> probably by inhibiting the production of interleukin-2. This immunological action suggests that calcipotriol may be useful in other conditions, such as contact dermatitis, skin cancers, and pityriasis rubra pilaris. Trials are also under way in Darier's disease and the ichthyoses. We will hear more of calcipotriol.

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